Applicants note with appreciation the withdrawal of the previous rejection under 35 U.S.C. §112, first paragraph, as this rejection was not reiterated.

Overview of the Above Amendments:

Claims 38, 39, 42 and 43 have been cancelled without prejudice and disclaimer. Applicants expressly reserve their right to bring the claims again in a related application.

Claim 37 has been amended to recite the subject invention with greater particularity and in order to respond to the rejection under 35 U.S.C. §112, second paragraph. Specifically, claim 37 now recites that the leukotoxin portion of the chimeric protein "activates" helper T-cells. Further, the claim now specifies that the chimeric protein comprises a selected "peptide hormone which is not a cytokine."

Support for these amendments can be found in the previous claims, as well as throughout the specification at, *inter alia*, page 8, lines 11-12; page 8, lines 15-16; and pages 17-18, bridging paragraph. Accordingly, no new matter has been added to the application by way of these amendments.

The foregoing amendments are presented at this time in order to place the application in condition for allowance. A new search is not believed to be necessary because the term "peptide hormone" is captured by the definition of antigen set forth in the application. See, e.g, page 8, lines 11-12. Further, GnRH, recited in claim 40, is a peptide hormone. Accordingly, the previous searches carried out by the Office should have identified art relevant to this recitation. Entry of the foregoing amendments at this time is therefore respectfully requested.

The Sequence Listing:

Applicants are providing a Sequence Listing with this response to substitute for that previously submitted when the application was filed. The Sequence Listing submitted herewith is the same as that provided with the direct parent to this application, U.S. Serial No. 08/455,970. The previously submitted Sequence Listing corresponds to

that provided in the grandparent application. A review of the Preliminary Amendment submitted when the application was filed makes clear that applicants intended to provide the present Sequence Listing but inadvertently provided the Sequence Listing from the grandparent application. Applicants apologize for the inadvertent error and request that the accompanying Sequence Listing now be entered.

Request to Withdraw Finality:

Applicants note that the present Office Action has been made final. However, the rejection under 35 U.S.C. §103 over U.S. Patent No. 5,476,657 to Potter et al. (Potter 1) in view of U.S. Patent No. 5,114,711 to Bell et al. (Bell) does not appear to be based on the claimed subject matter in the present application. For example, page 7 of the Office Action, last sentence, states: "However, Potter does not particularly exemplify chimeric proteins comprising a leukotoxin derived from *P. haemolytica* and gamma-interferon or active fragment thereof." None of the pending claims are directed to such an embodiment. Further, Bell is characterized as specifically disclosing that "cytotoxins and cytokines may be linked together to treat disease." Office Action, page 8. The Office therefore reasons: "It would have been obvious to one of ordinary skill in the art at the time the invention was made that gamma-interferon as disclosed by Bell et al. could be linked to at least one epitope of a leukotoxin derived from *P. haemolytica*, as taught by Potter." Again, such an embodiment is not presently claimed. Thus, clarification regarding this rejection is requested.

Additionally, applicants note that the above new ground of rejection was not necessitated by amendment of the claims by applicants. In particular, original claim 37 which in part formed the basis of the previous Office Action recited a "chimeric protein comprising a leukotoxin polypeptide coupled to a selected antigen." The amendment made to claim 37 in the response dated May 17, 1999 further characterized the nature of the leukotoxin polypeptide and did not place further limitations on the antigen. Based on the logic presented in the Office Action explained above, it appears the Office is basing

this rejection, at least in part, on the antigen component of the chimeric protein which was present in the previous claims. Further, the recitation of a leukotoxin polypeptide was also present in the previous claims.

Applicants note that Section 706.07(a) of the MPEP directs that a second or any subsequent action on the merits must not be made final where the examiner introduces a new ground of rejection not necessitated by amendment of the application by applicant, or by new art cited in an Information Disclosure Statement. Accordingly, applicants respectfully submit that the finality of the present Office Action is improper, and that the Office cannot now, in a final action, assert new grounds of rejection without giving applicants an opportunity to address the same. Such is an abridgment of applicants' right to due process.

For the foregoing reasons, applicants respectfully request withdrawal of the finality of the present Office Action.

The Double Patenting Rejections:

Claims 37, 40, 41, 44 and 45 were rejected under the judicially created doctrine of obviousness-type double patenting over claims 1, 2, 5, 6, and 9 of U.S. Patent No. 5,422,110, claims 1-23 of U.S. Patent No. 5,837,268 and claims 1-8 and 19-22 of U.S. Patent No. 5,723,129.

Applicants are submitting a Terminal Disclaimer with this response, thereby obviating these rejections.

Rejection Under 35 USC §112, Second Paragraph:

The Office rejected claims 37, 40, 41, 44 and 45 under 35 USC §112, second paragraph, as indefinite for the recitation "capable of." In particular, the Office requested that applicants present a positive recitation of function. Applicants have so done. Accordingly, this basis for rejection is believed to be overcome.

Rejections Under 35 USC §102:

Claims 37, 44 and 45 were rejected under 35 USC §102(b) as anticipated by U.S. Patent No. 5,476,657, to Potter ("Potter 1"). The Action asserts that Potter 1 discloses linking an antigen Pasteurella protein to a carrier and that "suitable carriers may be proteins, polysaccharides, VP6 polypeptides of rotaviruses, viral proteins..." (Office Action, page 5, emphasis in original). The Office further asserts: "These compositions would be structurally identical to those instantly claimed, i.e., a chimeric protein comprising leukotoxin coupled to an antigen." Office Action, page 6. However, applicants submit that the present claims indeed distinguish over Potter.

In particular, all of the examined claims recite that the leukotoxin polypeptide is coupled to a "peptide hormone." Potter 1 does not describe such an embodiment. Accordingly, this basis for rejection is believed to be overcome.

Additionally, claims 37, 44 and 45 were rejected under 35 USC §102(e) as anticipated by U.S. Patent No. 5,238,823, also to Potter ("Potter 2"). The Action argues that Potter 2 discloses the "expression of a fusion protein comprising leukotoxin having substantially the sequence of leukotoxin fused to IL-2 (a selected antigen) for use as a vaccine against shipping fever pneumoniae." Office Action, page 5. The Office appears to agree that claims which exclude cytokines would distinguish over Potter 2 and has requested that applicants expressly exclude cytokines from the claims, rather than relying on the definition in the specification. As explained above, the present claims now recite chimeric proteins wherein the leukotoxin polypeptide is coupled to a "peptide hormone." Further, in order to assure that a cytokine would not be construed as a peptide hormone, applicants have expressly eliminated cytokines from the claims. Thus, Potter 2 does not anticipate the present claims and this basis for rejection should also be withdrawn.

Rejections Under 35 USC §103:

Claims 37, 40, 41 and 45 were rejected under 35 USC §103(a), as being unpatentable over Potter (U.S. Patent No. 5,476,657) in view of Bell et al. (U.S. Patent

No. 5,114,711). The Office argues as above and, additionally, states: "Potter does not particularly exemplify chimeric proteins comprising a leukotoxin derived from *P. haemolytica* and gamma-interferon or active fragment thereof." Office Action, page 7. Bell is characterized as specifically disclosing that "cytotoxins and cytokines may be linked together to treat disease." Office Action, page 8. The Office therefore reasons: "It would have been obvious to one of ordinary skill in the art at the time the invention was made that gamma-interferon as disclosed by Bell et al. could be linked to at least one epitope of a leukotoxin derived from *P. haemolytica*, as taught by Potter." Applicants traverse this rejection.

As explained above, none of the pending claims are directed to the embodiment wherein gamma-interferon is linked to leukotoxin. In fact, as explained in response to the previous Office Action, such an embodiment is expressly excluded by virtue of the definition of antigen at page 8, lines 15-18 of the application.

Notwithstanding the above, applicants have now expressly specified that the antigen contemplated is not a cytokine. Thus, this basis for rejection no longer applies. Withdrawal thereof is respectfully requested.

Claims 37, 40, 44 and 45 were again rejected under 35 USC §103, as being unpatentable over any one of Lorberboum-Galeski et al., *Proc. Nat. Acad. Sci. USA* (1988) 85:1922-1926 ("Lorberboum-Galeski"), Williams et al., *Protein Engineering* (1987) 1:493-498 ("Williams"), U.S. Patent No. 4,675,382 to Murphy ("Murphy"), or U.S. Patent Nos. 4,935,233 to Bell et al. ("Bell 1") and 5,114,711 to Bell et al. ("Bell 2"), in view of Highlander et al., *DNA* (1989) 8:15-28 ("Highlander"), Strathdee et al., *J. Bacteriol.* (1989) 171:916-928 ("Strathdee") or Lo et al., *Infect. Immun.* (1985) 50:667-671 ("Lo") and further in view of U.S. Patent No. 5,028,423 to Prickett ("Prickett").

The Office contends that each of the primary references, Lorberboum-Galeski, Williams, Murphy, Bell 1 and Bell 2, discloses the recombinant production of a protein comprising a cytokine and various different cytotoxins. The secondary references are said to describe the leukotoxin gene from *P. haemolytica* and the tertiary reference,

Prickett, is alleged to disclose immunogenic conjugates comprising small peptide regions of leukotoxins. Applicants respectfully disagree with this rejection.

In particular, as previously explained to the Office, each of the cited primary references pertains to attachment of a cytokine to a cytotoxin. The purpose of creating the composite molecules of the primary references was to increase the cytotoxicity of the toxic component. Applicants, on the other hand, wish to elicit an enhanced immune response toward a selected antigen, in particular, a peptide hormone, in order to provide an immune response against the molecule. The chimeric proteins of the invention comprise an RTX leukotoxin polypeptide coupled to the peptide hormone. Cytokines are explicitly excluded from the definition of antigen at page 8, lines 15-18. The leukotoxin portion of the chimeric molecule of the present invention serves as an immune response potentiator, not as a toxic component, by providing T-cell epitopes for activating helper T-cells in order to enhance immunity to the peptide hormone.

This is in sharp contrast to the fusion proteins and chemical conjugates described in the cited art. These references teach how to kill cells with cytotoxic proteins. There is absolutely no hint in any of the primary references that the systems could be used to enhance the immunogenicity of a selected antigen.

With respect to the secondary references, applicants note that those references pertain to cloning *P. haemolytica* leukotoxin. None of the references suggest combining the resultant leukotoxin with a peptide hormone that is not a cytokine, in order to enhance an immune response.

Prickett (the tertiary reference) does not provide the missing link. Prickett pertains to chemical conjugates of small peptide fragments of leukotoxin to conventional carrier proteins, such as albumins and globulin fractions. (See column 3, lines 24-33). The leukotoxin is clearly not acting as an immunological carrier in this context. Accordingly, applicants submit that, when the cited references are considered in their entirety for what they fairly teach to one of ordinary skill in the art, none of the references, alone or in any combination, provides the requisite suggestion for a chimeric

protein comprising a leukotoxin molecule coupled to a peptide hormone for enhancing the immunogenicity of the peptide hormone.

Should the Office be relying on inherent properties of the molecules of the prior art in making this rejection, such is improper. As the Federal Circuit has cautioned, the inherency of a characteristic in a compound does not make it obvious. As stated by the Federal Circuit in *In re Newell*, 13 USPQ2d 1248 (Fed. Cir. 1989):

> [A] retrospective view of inherency is not a substitute for some teaching or suggestion which supports the selection and use of the various elements in the particular claimed combination...It is well established that in deciding that a novel combination would have been obvious, there must be supporting teaching in the prior art. 'That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.'

Newell at 1250, citing *In re Spormann*, 150 USPQ 449, 452 (CCPA 1966). Accordingly, to base an obviousness rejection on what the reference might inherently teach is wholly improper. For this reason alone, the rejection should be withdrawn.

Notwithstanding the above, applicants have amended the claims to expressly exclude cytokines, as requested by the Office. Thus, this basis for rejection is believed to be overcome. Reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. §103 is therefore respectfully requested.

Conclusion

Applicants respectfully submit that the claims define an invention which is novel and nonobvious over the art. Accordingly, allowance is believed to be in order, and an early notification to that effect would be appreciated.

If the Examiner notes any further matters which she believes may be expedited by a telephone interview, she is requested to contact the undersigned attorney at (650) 325-7812.

Respectfully submitted,

Date: 1/6/2000

By: _____
Roberta L. Robins
Registration No. 33,208

ROBINS & ASSOCIATES
90 Middlefield Road, Suite 200
Menlo Park, CA 94025
Telephone: (650) 325-7812
Fax: (650) 325-7823